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The Impact of Venous Thromboembolism on Upper Tract Urothelial Carcinomas undergoing Open or Minimally-Invasive Radical Nephroureterectomy in the United States: Perioperative Outcomes and Health-care Costs from Insurance Claims Data

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Abstract

Background and Objective: Venous thromboembolism (VTE) constitutes a significant predictor of worse postoperative morbidity in cancer surgeries. There has been no data available for patients with preoperative VTE and upper tract urothelial carcinoma (UTUC) undergoing radical nephroureterectomy (RNU). Our aim was to assess the impact of a preoperative VTE diagnosis on perioperative outcomes in the RNU context.

Methods: Patients aged 18 or older with an UTUC diagnosis undergoing RNU were identified in the Merative™Marketscan® Research de-identified databases between 2007-2021. Multivariable logistic regression adjusted by relevant perioperative confounders was used to investigate the association between diagnosis of VTE prior to RNU and 90-day complication rates, postoperative VTE, re-hospitalization, and total costs. Sensitivity analysis on VTE severity (pulmonary embolism [PE] and/or deep venous thrombosis [DVT]) was examined.

Key Findings and Limitations: Within the investigated cohort of 6,922 patients, history of any VTE preceding RNU was reported in 568 (8.21%) cases, including DVT (n=290, 51.06%), PE (n=169, 29.75%), and superficial VTE (n=109, 19.19%). The history of VTE before RNU was predictive of higher rates of complications, the most prevalent being respiratory (OR: 1.78, 95%CI: 1.43-2.22). Preoperative VTE was found to be associated with an increased risk of VTE following RNU (OR: 14.3, 95%CI: 11.48-17.82), higher re-hospitalization rates (OR: 1.26, 95% CI 1.01-1.56), other than home discharge status (OR: 1.44, 95%CI: 1.18-1.77), and higher costs (OR 1.42, 95%CI: 1.20-1.68). Limitations include the retrospective nature and the use of an insurance database which relies on accurate coding and does not include information such as pathologic staging.

Conclusions and Clinical Implications: The presented findings will contribute to the counseling process for patients. These patients may benefit from enhanced pre/postoperative anticoagulation. More research is needed before the following results can be used in the clinical setting.

Keywords

radical nephroureterectomy; venous thromboembolism; pulmonary embolism; deep venous thrombosis; perioperative morbidity; health-related costs

1.0 Introduction

Upper tract urothelial carcinoma (UTUC) affects less than 2 per 100,000 people and comprises approximately 5% of urothelial tumors. The mainstay of treatment for these patients includes radical nephroureterectomy (RNU) with an ipsilateral bladder cuff.[1-3]

Most of the early literature has focused on the surgical approach with the increasing performance of laparoscopic and robotic surgery as well as predictors of complications. In these manuscripts, venothrombolic events (VTE) were never factored in as predictors of complications, but were notable as postoperative complications.[1, 3]

VTE consists of both pulmonary embolism (PE) and deep vein thrombosis (DVT), both of which have consequences for patients. The relationship between malignancy and VTE has been thoroughly documented and VTE is the leading cause of non-cancer deaths in patients undergoing cancer surgery as well as a significant source of morbidity, mortality and hospital costs.[4-8] To date, there have been no publications on VTE as a preoperative predictor of morbidity and hospital costs in patients undergoing RNU. Given this, our aim was to assess the health-related outcomes of VTE in patients with UTUC and VTE undergoing RNU. Our hypothesis is that these patients with known VTE will likely have increased rates of morbidity and hospital costs following intervention with RC.

2.0 Materials and Methods

2.1 Data source

The present research is a retrospective cohort analysis based on administrative insurance claims data from the Merative™Marketscan® Research Commercial and Medicare databases (DOI: 10.57761/kg3j-nh50). The database consists of individual-level, de-identified, demographic data, diagnoses, procedures, overall health-related costs, and inpatient and outpatient pharmacy billing claims and treatments allowing for longitudinal tracking of patients. International Classification of Disease Ninth and Tenth Revisions, Clinical Modification (ICD-9-CM, ICD-10-CM) codes, and Current Procedural Terminology (CPT) codes were used to identify the cohort of interest, treatments, and comorbidities. This method has been used in other studies[9-18] and given the de-identified information, the study was deemed exempt from informed consent requirements by the Stanford University Medical Center Institutional Review Board. Data for this project was accessed using the Stanford Center for Population Health Sciences (PHS) Data Core. The PHS Data Core is supported by a National Institutes of Health National Center for Advancing Translational Science Clinical and Translational Science Award (UL1TR003142) and from Internal Stanford funding.

2.2 Patients

Using ICD-9/10-CM and CPT diagnosis/treatment codes for UTUC and RNU, data of patients aged at least 18 years who underwent RNU by open or minimally invasive (MIS) approach (i.e., conventional or robot-assisted laparoscopic RNU) for UTUC treatment between 2007-2021 were reviewed. Patients selected for analysis were enrolled in the database for at least 3 months before and 3 months following their initial UTUC diagnosis. The RNU date was designated as the index date for further assessment. Within this cohort, diagnosis codes were identified and reviewed to ensure the selection of patients with a history of preoperative VTE, defined as PE, DVT, or phlebitis/thrombophlebitis. The study cohort was further stratified into sub-groups based on the presence of VTE before RNU ("*Pre-VTE*") vs. no history of VTE before RNU ("*Non-pre-VTE*"). For

each patient, sociodemographic data was initially recorded. Further, clinical characteristics of patients, encompassing the Charlson Comorbidity Index (CCI) score,[19,20] specific comorbidity prevalence, outpatient prescriptions for chemoprophylaxis (anticoagulants), and antibiotic prophylaxis, were recorded. Treatment characteristics included the RNU approach (open vs. MIS) and perioperative procedures and modalities relevant to RNU, such as administration of neoadjuvant and/or adjuvant chemotherapy (NAC, AC) and prior external-beam radiation therapy. A flow chart diagram summarizing the analytical steps for the data analysis and inclusion/exclusion criteria was shown in Supplemental Figure 1 and a detailed list of ICD-9/10 and CPT codes was presented in Supplementary Table 1. The flow chart diagram together with the selected inclusion/exclusion criteria was able to equally distribute demographic predictors and risk factors associated with the VTE events and the UTUC/RNU diagnosis/procedures thus eliminating the necessity for propensity score matching adjustments.

2.3 Outcome Ascertainment

The primary objective of the study was to determine the impact of preoperative VTE events on perioperative outcomes and costs. To address these issues, we examined the impact of VTE diagnosis prior to RNU on 90-day postoperative complications and novel VTE events, median in-hospital length of stay (LOS), discharge status to self-care/home vs. any other medical facility, readmission rates, and total healthcare costs associated with the entire RNU recovery. The measurement of costs covered a combination of 90-day direct hospital costs together with any potentially accountable perioperative interventions, along with adverse events resulting from the index surgery, adjusted to 2021 US dollars. The secondary aim of the study was to evaluate the differential effect of the severity of VTE, as categorized by PE, DVT, and phlebitis/thrombophlebitis, on the predetermined outcomes.

2.4 Statistical analysis

Continuous variables were reported using means ± standard deviations (SDs) or medians and interquartile ranges (IQR). Categorical variables were presented as counts and percentages (%). The statistical analysis involved using the Chi-square test for comparison of categorical data, the Student's t-test for age, and the Wilcoxon rank-sum test for other continuous variables, all stratified by preoperative VTE status. Multivariable logistic regression models were implemented to investigate the impact of VTE history on the probability of developing subsequent VTE or surgical complications following RNU. Perioperative outcomes, such as LOS and overall RNU costs, were tested by applying the median or 3rd quartile distribution as the reference threshold for logistic regression models. Subsequently, logistic regression analyses were replicated after sub-stratification for the degree of VTE severity (PE, DVT, or peripheral phlebitis) in order to explore if the association with perioperative outcomes remained consistent.

All multivariable models were adjusted by clinically relevant variables, including age, CCI score, obesity, NAC or AC administration, and surgical approach. All analyses were two-sided with, $p<0.05$ considered significant, and performed using statistical software SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

3.0 Results

3.1 Study cohort

The study covered a cohort of 6,922 individuals diagnosed with UTUC who underwent RNU between the years 2007-2021 in the US. Within the investigated population, 6,354 patients (91.79%) had no recorded evidence of preoperative VTE, whereas the positive history of VTE preceding RNU was present in 568 (8.21%) patients. DVT was the most prevalent type (n=290, 51.06%), followed by PE (n=169, 29.75%) and phlebitis/thrombophlebitis (n=109, 19.19%).

Table 1 lists the comparison of sociodemographic, clinical, and hospital characteristics in the analyzed cohort, divided according to the presence ("*Pre-VTE*") or absence ("*Non-pre-VTE*") of VTE events prior to RNU. The distribution of patients among the groups was equitable with respect to gender, insurance coverage, and US geographical region. Patients in the "*Pre-VTE*" group exhibited a slightly higher mean age compared to those in "*Non-pre-VTE*" group. Individuals with VTE prior to RNU had higher median CCI score. Those who were diagnosed with VTE before RNU were significantly more likely to suffer from associated comorbidities and receive preoperative anticoagulant prophylaxis (27.29% vs. 6.63%). Notably, a significant disparity in the adoption of the MIS approach was observed between the "*Pre-VTE*" and "*Non-pre-VTE*" groups, with a lower frequency of MIS reported in the former (47.89% vs. 64.37%). A difference in median follow-up duration between "*Pre-VTE*" and "*Non-pre-VTE*" groups, however statistically significant, was less than 6 months (median 1.56 years vs. median 2.01 years). Median time of preoperative VTE to RNU was 2.63 months with an IQR of 0.7-15.1.

3.2 Outcomes

3.2.1 VTE history and Intra- and 90-days postoperative sequalae—Respiratory, followed by digestive and infectious, were the predominant complications, with an incidence of 72.71%, 65.67%, and 38.56% in the "*Pre-VTE*" group. The descriptive and effect size estimates of VTE events on intra- and 90-day postoperative complications have been summarized and visually shown in Figure 1. Performing multivariable logistic regression analysis, history of VTE preceding RNU predicted higher rates of respiratory (aOR: 1.78, 95%CI: 1.43-2.22), digestive (aOR: 1.49, 95%CI: 1.22-1.82), infectious (aOR: 1.55, 95%CI: 1.29-1.85), and hemorrhagic (aOR: 2.49, 95%CI: 1.69-3.66) complications. The predictive effect of preoperative VTE was not observed for intraoperative, wound, urinary, and cardiac-related complications, which was possibly attributed to the very low frequency of these complications within the examined cohort. Similar trends were observed for digestive, respiratory, and infectious complications regardless of the degree of VTE severity (Supplementary Table 2).

Additionally, on multivariable analysis, preoperative diagnosis of VTE is the most influential factor in predicting the occurrence of novel VTE events following RNU. This finding was consistent across all analyses, either in the case of any type of VTE (aOR: 14.3, 95%CI: 11.48-17.82, Figure 1) or separately with regards to specific VTE types,

including PE (aOR: 37.25, 95%CI: 26.38-52.6), DVT (aOR: 11.77, 95%CI: 8.88-15.59), and thrombophlebitis (aOR: 3.36, 95%CI: 1.81-6.25) (Supplementary Table 2).

3.2.2 VTE history, LOS, Discharge status, and Re-hospitalization—Patients with a history of preoperative VTE had a considerably longer median LOS compared to individuals without VTE prior to RNU (median 5 [IQR: 3-8] vs. median 3 [IQR: 2-5]). Multivariable logistic regression analysis revealed an increased risk for prolonged hospitalization in cases of preoperative VTE when setting both the median (aOR: 1.76, 95%CI: 1.47-2.09, Figure 2) and the 3rd quartile distribution threshold (aOR: 2.29, 95%CI 1.86-2.82). After sub-stratification for the degree of VTE severity (Supplementary Table 2), correlation with prolonged hospitalization was substantiated only in cases of PE (aOR: 2.64, 95%CI: 1.74-4.03) or DVT (aOR: 2.21, 95%CI: 1.61-3.02).

Furthermore, a statistically significant disparity was found between the "*Pre-VTE*" and "*Non-pre-VTE*" groups in terms of discharge status, as a notably higher proportion of patients in the former group (26.41%) were discharged to other medical facilities (i.e., hospice medical facilities, federal facilities, short-term hospitals) rather than home/self-care, compared to the latter group (16.51%). A history of VTE prior to RNU was significantly associated with an increased probability of being discharged elsewhere rather than home/self-care in case of any VTE events (aOR: 1.44, 95%CI: 1.18-1.77, Figure 2) and irrespective of the VTE severity type (Supplementary Table 2).

The rates of re-hospitalization within 90 days following RNU were reported to be slightly higher in patients with a preoperative VTE diagnosis than in individuals without a history of VTE before RNU (21.48% vs. 16.51%). As predicted, patients with VTE prior to RNU had a higher probability of experiencing re-hospitalization in case of any VTE events (aOR: 1.26, 95%CI 1.01-1.56, Figure 2) and PE (aOR: 1.74, 95%CI: 1.23-2.46, Supplementary Table 2). However, no association was found between the occurrence of preoperative DVT/peripheral phlebitis/thrombophlebitis and increased re-hospitalization rates (Supplementary Table 2).

3.2.3 VTE history and Total Hospital Costs—The calculated median healthcare cost for patients with recorded VTE prior to RNU was $32,579, which was significantly increased compared to patients with no history of preoperative VTE ($25,333). The history of VTE events prior to RNU was found to be associated with an increased probability of being higher than the median cost (aOR 1.42, 95%CI: 1.20-1.68, Figure 2). The observed effect of preoperative VTE on cost was even more pronounced when setting the threshold at the 3rd quartile distribution for total hospital expenditures (aOR: 1.83, 95%CI: 1.52-2.19). After sub-stratification for the degree of VTE severity (Supplementary Table 2), the same increased risk for higher hospital costs was substantiated only in cases of PE (aOR: 1.91, 95%CI: 1.38-2.65) or DVT (aOR: 1.73, 95%CI: 1.35-2.22), whereas not in cases of thrombophlebitis.

4.0 Discussion

To our knowledge, this study represents the sole publication that has evaluated the risks associated with history of preoperative VTE on RNU outcomes. Our retrospective cohort analysis revealed that patients undergoing RNU with a known history of VTE had increased morbidity, hospital LOS, discharge to other than home/self-care facilities, readmission rates, probability of postoperative VTE, and hospital costs.

With regards to literature published looking at preoperative VTE as a risk factor, this has been examined in patients undergoing radical nephrectomy and partial nephrectomy, but not RNU. Those patients were found to have increased risks of morbidity, mortality and ICU admissions.[8] There additionally has been a study using the NSQIP database from 2006-2012 comparing all complication rates in patients undergoing laparoscopic nephroureterectomy (LNU) in comparison to nephrectomy which found that LNU had higher overall risk of complications (RR 1.41, 95% CI 1.16–1.72). They found that older age, ASA class 3 - 5, elevated creatinine, and transfusions of more than 4 units of red blood cells were associated with higher complication rates.[21] They did not evaluate however for VTE as a preoperative risk factor for complications. In the present study, our findings indicated that history of VTE prior to RNU, particularly PE or DVT, was associated with elevated rates of overall, as well as respiratory, digestive, and infectious, complications.

As previously stated, the association between cancer and VTE is widely recognized.[22] In the existing literature that examines urological procedures, the primary focus has predominantly concentrated on cystectomy, prostatectomy, and nephrectomy, but not RNU.[23,24] In our study, we show that individuals who had PE and underwent RNU exhibited a substantial elevation in the probability of experiencing postoperative PE (aOR 37.19, 95%CI: 26.34-52.52). Similarly, patients with preoperative DVT also demonstrated a significant rise in the risk of DVT (aOR 11.87, 95%CI: 8.96-15.73) following RNU. Considering the well-documented morbidity and mortality rates linked with VTE, it is imperative to acknowledge the significance of these findings.[25,26]

RNU is a procedure that is not without complications requiring subsequent readmissions. In a retrospective study conducted by Geiger *et al.* published in 2020, the authors examined a cohort of 596 patients who underwent RNU at seven academic centers throughout the period of 2005-2015. The study investigated variables associated with prolonged LOS and readmissions after RNU and showed that patients in the upper quartile of CCI scores had an elevated LOS and a higher probability of hospital readmission.[27] In our research, we adjusted for CCI in multivariable analyses and found that patients with preoperative PE and DVT still exhibited an elevated risk of readmissions (aOR 1.47, 95%CI: 1.21-1.79; aOR 1.3, 95%CI: 1.11-1.52) and a prolonged hospital LOS (aOR 2.6, 95%CI: 1.71-3.96; aOR 2.16, 95%CI: 1.58-2.96). Additionally, the existing body of literature on costs related to the management of UTUC is limited. The majority of the available research primarily concentrates on the financial implications related to surgical approach.[28-30] Our results indicate that patients with UTUC who experienced preoperative VTE characterized by both PE and DVT, exhibited substantially higher healthcare costs related to RNU, even after accounting for variables such as surgical approach (open vs. MIS) and CCI score (aOR

1.92, 95%CI: 1.39-2.67; aOR 1.74, 95%CI 1.36-2.23). These findings are not surprising, considering the increased rates of complications and readmissions observed in patients with VTE prior to RNU.

This is the first publication to our knowledge in this area. Although novel, this study is not devoid from limitations. Our paper is retrospective in nature and relies on claims data and codes which do not allow for the same scrutiny as a prospective study and is vulnerable to inaccuracies especially in relation to coding errors. Additional limitations include patients diagnosed with preoperative VTE were likely symptomatic and this data may underpredict the number of patients with preoperative VTE. A limitation of the Marketscan database is that it does not contain any pathologic or tumor-specific information which would likely influence some of the outcomes evaluated in the study. Lastly, given that this data obtained for this study originates from an insurance database, it may not be a complete accurate representation of the entire US or the global population.

5.0 Conclusions

Patients with preoperative VTE undergoing RNU have increased morbidity, post procedure VTE, hospital LOS, rehospitalizations and increased hospital costs. The presented findings will contribute to the counseling process for patients with UTUC and preoperative VTE by providing enhanced insights into the risks associated with surgery in order to effectively manage and minimize these risks. Additionally, these patients may benefit from enhanced pre and postoperative anticoagulation. More research is needed before the following results can be used in the clinical setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

6.0 References

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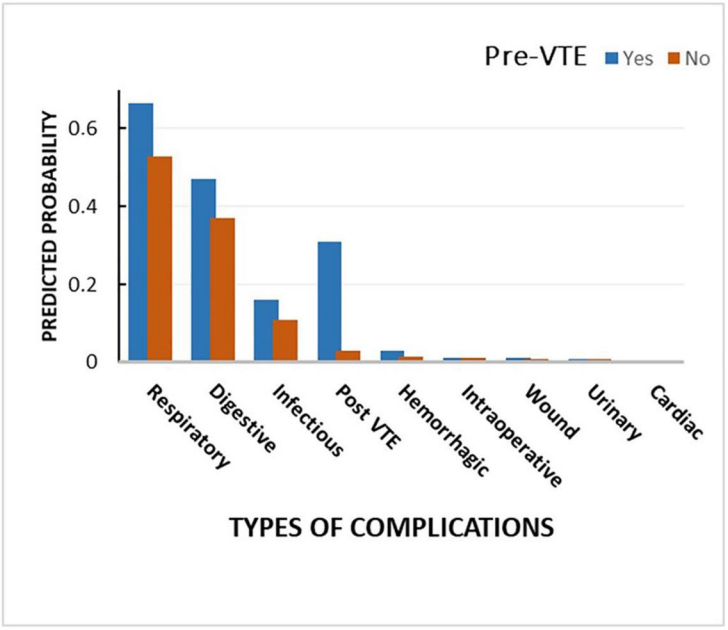
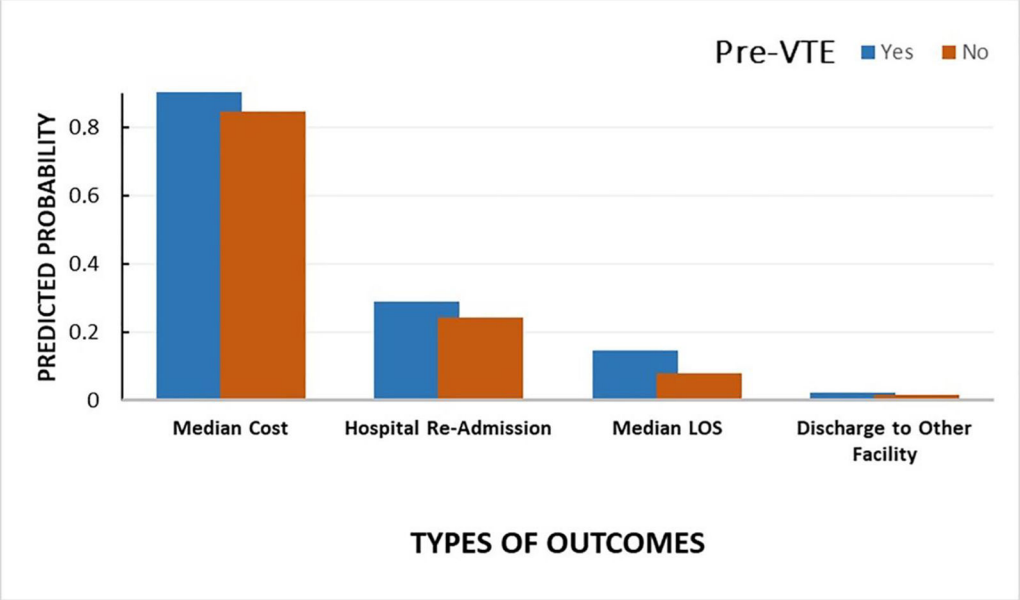


Complications, n (%)	**Non-pre-VTE**	**Pre-VTE**	***p-value***	**aOR** (95%CI)	***p-value***
Respiratory	3978 (62.61)	413 (72.71)	*<.0001*	1.78 (1.43 - 2.22)	*<.0001*
Digestive	3666 (57.7)	373 (65.67)	*0.0002*	1.49 (1.22 - 1.82)	*0.0001*
Infectious	1755 (27.62)	219 (38.56)	*<.0001*	1.55 (1.29 - 1.85)	*<.0001*
Hemorrhagic	132 (2.08)	30 (5.28)	*<.0001*	2.49 (1.69 - 3.66)	*<.0001*
Intraoperative	58 (0.91)	<11	*0.732*	1.12 (0.51 - 2.47)	*0.7826*
Wound	114 (1.79)	18 (3.17)	*0.0217*	1.59 (0.95 - 2.65)	*0.0758*
Urinary	46 (0.72)	<11	*1*	0.88 (0.35 - 2.23)	*0.7946*
Cardiac	24 (0.38)	<11	*0.0842*	1.91 (0.72 - 5.10)	*0.1962*
Postoperative VTE, n (%)				14.3 (11.48 - 17.82)	*<.0001*
All new VTE	234 (3.68)	217 (38.2)	*<.0001*		
PE	84 (1.32)	97 (17.08)	*<.0001*		
DVT	145 (2.28)	138 (24.30)	*<.0001*		
Thrombo-/phlebitis	75 (1.18)	49 (8.63)	*<.0001*		

Figure 1.

Predicted probability plots, and multivariable logistic regression estimates for the specific 90-days postoperative complications.

VTE: venous thromboembolism; **aOR**: adjusted Odds Ratio; **CI**: confidence interval; **n**: number; **PE**: pulmonary embolism; **DVT**: deep venous thrombosis.



Outcomes	Non-pre-VTE	Pre-VTE	*p-value*	aOR (95%CI)	*p-value*
Median costs, median $ (IQR)	25,333 (16,820 - 40,306)	32,579 (17,475 - 59,134)	*<.0001*	1.42 (1.20 - 1.68)	*<.0001*
1st Quartile	1597 (25.13)	133 (23.42)	*<.0001*		
2nd Quartile	1643 (25.86)	88 (15.49)			
3rd Quartile	1600 (25.18)	131 (23.06)			
4th Quartile	1514 (23.83)	216 (38.03)			
Length of stay, median days (IQR)	3 (2-5)	5 (3-8)	*<.0001*	1.76 (1.47 - 2.09)	*<.0001*
1st Quartile	1676 (30.82)	85 (17.97)	*<.0001*		
2nd Quartile	1131 (20.80)	58 (12.26)			
3rd Quartile	1484 (27.29)	128 (27.06)			
4th Quartile	1147 (21.09)	202 (42.71)			
Re-hospitalization, 90-days	1049 (16.51)	122 (21.48)	*0.0025*	1.26 (1.01 - 1.56)	*0.0384*
Discharge status, n (%)			*<.0001*	1.44 (1.18 - 1.77)	*0.0004*
Home/self-care	5177 (81.48)	418 (73.59)			
Other facilities	1177 (18.52)	150 (26.41)			
Any 90-day complications, n (%)	681 (10.72)	100 (17.61)	*<.0001*	1.46 (1.16 - 1.85)	*0.0016*

Figure 2.

Predicted probability plots, and multivariable adjusted logistic regression estimates for the risk of prespecified outcomes.

VTE: venous thromboembolism**; IQR**: interquartile range**; aOR**: adjusted Odds Ratio; **CI**: confidence interval; **n**: number; **LOS**: length of stay; **PE**: pulmonary embolism; **DVT**: deep venous thrombosis.

Table 1.

Baseline patient demographic, clinical and hospital characteristics of the final cohort of the study according to VTE history prior to RNU (non-pre-VTE vs. pre-VTE).

VTE: venous thromboembolism; **PE**: pulmonary embolism; **DVT**: deep venous thrombosis; **SD**: standard deviation; **IQR**: interquartile range; **n**: number; **US**: United States; **HMO**: Health Maintenance Organization; **PPO**: Preferred Provider Organization; **CCI**: Charlson Comorbidity Index; **MIS**: minimally invasive surgery; **RNU**: radical nephroureterectomy; **NAC/AC**: neoadjuvant/adjuvant chemotherapy.

Variables	**Non-pre-VTE n = 6354 (91.79)**	**Pre-VTE n = 568 (8.21)**	***p-value***
Preop. VTE diagnosis, n (%)			
PE	NA	169 (29.75)	
DVT	NA	290 (51.06)	
Thrombo-/phlebitis	NA	109 (19.19)	
Age, mean (SD)	61.76 (12.59)	64.49 (11.97)	*<.0001*
1st Quartile	1552 (24.43)	96 (16.9)	*<.0001*
2nd Quartile	1749 (27.53)	142 (25)	
3rd Quartile	1479 (23.28)	162 (28.52)	
4th Quartile	1574 (24.77)	168 (29.58)	
Follow up years, median (IQR)	2.01 (0.25 - 14.73)	1.56 (0.25 - 14.62)	*<.0001*
Time (months) from Preop. VTE to RNU, median IQR	N/a	2.63 (0.7-15.1)	
Gender, n (%)			
Male	3929 (61.84)	359 (63.2)	*0.5196*
Female	2425 (38.16)	209 (36.8)	
US region, n (%)			
Northeast	1372 (21.59)	131 (23.06)	*0.4483*
North Central	1509 (23.75)	140 (24.65)	
South	2281 (35.9)	193 (33.98)	
West	1051 (16.54)	>90	
Unknown	141 (2.22)	<11	
Data source, n (%)			
Fee for Service	3623 (57.02)	285 (50.18)	*0.0022*
Encounter	490 (7.71)	38 (6.69)	
Medicare	1956 (30.78)	222 (39.08)	
Medicare Encounter	274 (4.31)	22 (3.87)	
Insurance type, n (%)			
Comprehensive	969 (15.25)	118 (20.77)	*0.0041*
HMO	718 (11.3)	54 (9.51)	
PPO	3494 (54.99)	289 (50.88)	
Other	1173 (18.46)	107 (18.84)	
CCI, median (range)	3 (0 - 20)	5 (0 - 18)	*<.0001*
0-1	798 (12.56)	37 (6.51)	*<.0001*
2-4	3624 (57.03)	221 (38.91)	
≥5	1932 (30.41)	310 (54.58)	

Variables	Non-pre-VTE n = 6354 (91.79)	Pre-VTE n = 568 (8.21)	*p-value*
RNU surgical approach, n (%)			
Open RNU	2264 (35.63)	296 (52.11)	*<.0001*
Laparoscopic/Robot-assisted RNU	4090 (64.37)	272 (47.89)	
Prevalent comorbidities, n (%)			
Obesity	872 (13.72)	113 (19.89)	*<.0001*
Diabetes	1804 (28.39)	180 (31.69)	*0.0958*
Hypertension	4258 (67.01)	443 (77.99)	*<.0001*
Cardio-vascular	5110 (80.42)	554 (97.54)	*<.0001*
Renal failure	1313 (20.66)	182 (32.04)	*<.0001*
Smoking	1056 (16.62)	95 (16.73)	*0.9482*
Infectious	1900 (29.9)	240 (42.25)	*<.0001*
Neoplasms	5748 (90.46)	529 (93.13)	*0.0359*
Endocrine	4894 (77.02)	480 (84.51)	*<.0001*
Hematologic	1938 (30.5)	304 (53.52)	*<.0001*
Nervous	1719 (27.05)	242 (42.61)	*<.0001*
Respiratory	4186 (65.88)	453 (79.75)	*<.0001*
Digestive	3970 (62.48)	419 (73.77)	*<.0001*
Genitourinary	6159 (96.93)	549 (96.65)	*0.7156*
Dermatologic	2894 (45.55)	330 (58.1)	*<.0001*
Musculoskeletal	4495 (70.74)	474 (83.45)	*<.0001*
Congenital	896 (14.1)	107 (18.84)	*0.0021*
Antibiotics prescriptions, n (%)			
90-days before RNU	2686 (42.27)	241 (42.43)	*0.9422*
90-days after RNU	2461 (38.73)	214 (37.68)	*0.6206*
Anticoagulant prophylaxis, n (%)			
90-days before RNU	421 (6.63)	155 (27.29)	*<.0001*
90-days after RNU	558 (8.78)	181 (31.87)	*<.0001*
External-beam radiation, n (%)			
90-days before RNU	62 (0.98)	<11	*0.5553*
90-days after RNU	181 (2.85)	27 (4.75)	*0.0108*
Systemic chemotherapy, n (%)			
NAC	164 (2.58)	34 (5.99)	*<.0001*
AC	521 (8.20)	60 (10.56)	*0.0516*
Previous intravesical therapy, n (%)			
90-days before RNU	29 (0.46)	<11	*0.8091*
90-days after RNU	72 (1.13)	<11	*0.831*